

On the rupture of DNA molecule

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Using Langevin Dynamic simulations, we study effects of the shear force on the rupture of a double stranded DNA molecule. The model studied here contains two single diblock copolymers interacting with each other. The elastic constants of individual segments of the diblock copolymer are considered to be different. We showed that the magnitude of the rupture force depends on whether the force is applied at 3' – 3'-ends or 5' – 5'-ends. Distributions of extension in hydrogen bonds and covalent bonds along the chain show the striking differences. Motivated by recent experiments, we have also calculated the variation of rupture force for different chain lengths. Results obtained from simulations have been validated with the analytical calculation based on the ladder model of DNA.

PACS numbers:

I. INTRODUCTION

Separation of a double stranded DNA (dsDNA) is prerequisite for the essential cellular processes, such as, replication and transcription [1]. It is now well understood that DNA is stabilized by inter- and intra- molecular interactions [1–3]. Single Molecular Force Spectroscopy (SMFS) techniques, e.g., optical tweezers, magnetic tweezers and atomic force microscopy, have emerged as powerful tools to investigate these interactions [3–13]. These experiments have provided various insights and understanding of biological processes at the molecular level. Moreover, experiments which explored the functioning of these interactions [3–13] revealed that not only the magnitude of the force is important, but the nature of force, how and where force is applied, is also important in the understanding of the biological processes. To study DNA unzipping, a force has been applied perpendicular to the helix direction [4, 5]. The unzipping force was found to be ≈ 15 pN. In another experiment, the force is applied along the helical axis [6], and rupture of DNA has been studied. The rupture force is found to be significantly different than the unzipping force. Strunz *et al.* [7, 8] observed that the rupture force depends on the length of DNA and the loading rate. The dynamics of dissociation of two strands was also investigated [14]. Hatch *et al.* [10] have performed systematic experiments on different lengths of DNA, and showed that the rupture force increases linearly for small chain lengths, but saturates at higher lengths.

To understand these observations, different models of DNA have been proposed to explain the dynamics of DNA. Singh *et al.* [15] used a lattice model of dsDNA,

and showed that the rupture force increases with the length of DNA. Expressing the covalent and hydrogen bond as harmonic springs, de Gennes [16] proposed that the net shear force required to rupture a homosequence dsDNA of length l is

$$f_c = 2f_1(\chi^{-1} \tanh(\chi \frac{l}{2})), \quad (1)$$

where f_1 is the force required to break a single base-pair. Here, χ^{-1} is the de Gennes characteristic length which is defined as

$$\chi^{-1} = \sqrt{\frac{Q}{2R}}, \quad (2)$$

where Q and R are spring constants of covalent and hydrogen bonds respectively. Equation 1 shows that the shear force increases linearly with l (for small lengths), and saturates at higher values of l , which is consistent with the experiment [10]. Different models similar to the ladder model have been studied and explored the different aspects of DNA rupture [17–20].

In other experiments [21, 22], the force-extension curve of a single strand DNA consists of only Thymine (poly T) (or Uracil (poly U) in RNA) shows the entropic response, whereas Adenine (poly A) shows plateaus because of the base stacking. As a result, the force-extension curves of these strands are found to be strikingly different [21, 22]. Thus, use of different elastic constants for the complementary strands in the model studies is prerequisite. Interestingly, theoretical models have used the same elastic constant for both strands in their description [16–18].

Recently, Nath *et al.* [23] studied the DNA rupture using the ladder model, where the elastic constants of

complementary strands were different. Their results were in good agreement with the atomistic simulations. However, because of the symmetry, the rupture forces applied at $3' - 3'$ and $5' - 5'$ -ends will be the same. In contrast, Danilowicz *et al.* [11] have observed structural changes, when a force is applied at $3' - 3'$ -ends and $5' - 5'$ -ends, and the rupture force was found to be different. One of the possible reasons may be that the chain is heterosequence in nature, whereas theoretical models consider homosequence chain.

The simplest way to include heterogeneity in the ladder model is to consider a single strand made up of a diblock copolymer, i.e., half of the strand consists T type of nucleotides (say) and other half is of A type nucleotides (Fig. 1). In complementary strand, the first half consists of A type nucleotides, whereas second half is made up of T type nucleotides. The elastic constant Q of the segment consists of A is different than the elastic constant U of the segment consists of T. It is obvious from the Fig. 1 that the shearing force may be applied either at the ends having nucleotides (A) of spring constants (Q-Q) (say, $3' - 3'$) or at the ends of nucleotides (T) having spring constants (U-U) ($5' - 5'$) [24].

The aim of this paper is to study the structural changes and to calculate the rupture force applied at the $3' - 3'$ and $5' - 5'$ -ends of dsDNA. In section II, we have developed a coarse grained model of DNA, and studied the dynamics of DNA under the shearing force using Langevin dynamic simulations. In section III, we showed that the rupture force depends on the ends where the shearing force is applied. In this section, we have also obtained the distributions of extension in stretching of covalent and of hydrogen bonds, which give important information about the structural changes. Section IV contains the analytical solution based on the ladder model of dsDNA consisting of a diblock sequence of DNA similar to the one developed in the Sec. II. The expressions for the force required for rupture have been obtained for both cases (Q-Q and U-U), which are in good agreement with the simulation results. The paper ends with a brief discussion on the results and future perspectives.

II. COARSE GRAINED MODEL OF DNA

A coarse grained model of two interacting flexible polymer chains in three dimension (3d) has been taken to model a dsDNA [18]. The single strand of DNA consists of two segments connected by a covalent bond. In fact, each segment consists of nucleotide of one type called

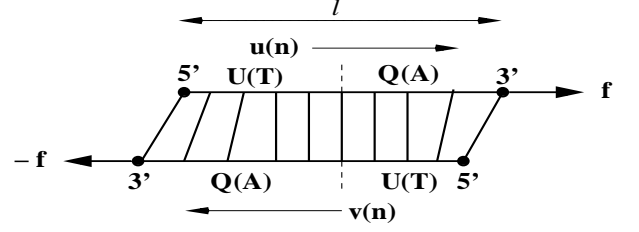


FIG. 1: Schematic diagram of a heterogeneous dsDNA preserving complementarity being pulled by a shear force.

bead, which is composed of several molecules, e.g., sugar, phosphate, hydrogen, nitrogen etc. The interaction between consecutive beads (covalent bonds) is modelled by harmonic potential. The Lennard Jones (LJ) potential is used to model the base-pairing interaction between nucleotides of complementary strands. The total energy of the model system can be expressed as:

$$\begin{aligned}
 E = & \sum_{l=1}^2 \sum_{j=1}^{N/2} k^{(l)} (\mathbf{r}_{j+1,j}^{(l)} - d_0)^2 + \sum_{l=1}^2 \sum_{j=N/2}^N k^{(l)} (\mathbf{r}_{j+1,j}^{(l)} - d_0)^2 \\
 & + \sum_{l=1}^2 \sum_{i=1}^{N-2} \sum_{j>i+1}^N 4 \left(\frac{C}{|\mathbf{r}_{i,j}^{(l)}|^{12}} \right) + \sum_{i=1}^N \sum_{j=1}^N 4 \left(\frac{C}{(|\mathbf{r}_i^{(1)} - \mathbf{r}_j^{(2)}|)^{12}} \right. \\
 & \left. - \frac{A}{(|\mathbf{r}_i^{(1)} - \mathbf{r}_j^{(2)}|)^6} \delta_{ij} \right), \quad (3)
 \end{aligned}$$

where N is the number of beads in each strands. Here, $\mathbf{r}_i^{(l)}$ represents the position of the i^{th} bead on the l^{th} strand. In present case, $l = 1(2)$ corresponds to first (complementary) strand of dsDNA. The distance between intra-strand beads, $\mathbf{r}_{i,j}^{(l)}$, is defined as $|\mathbf{r}_i^{(l)} - \mathbf{r}_j^{(l)}|$. The first two terms of the above expression are the harmonic contributions from both strands. In the first term, the spring constant $k^{(1)} = U = 60$, whereas for the complementary strand $k^{(2)} = Q = 100$ for the first half of the dsDNA, i.e., $j = 1$ to $N/2$. The second term of above expression is the contribution of harmonic terms for the remaining half of the strands ($k^{(1)} = Q = 100$ and $k^{(2)} = U = 60$). Third term takes care of the excluded volume effect, i.e., two beads cannot occupy the same space [25]. The fourth term corresponds to the LJ potential, which takes care of the mutual interaction between the two strands. The first term of LJ potential (same as third term of Eq. (3)) will not allow the overlap

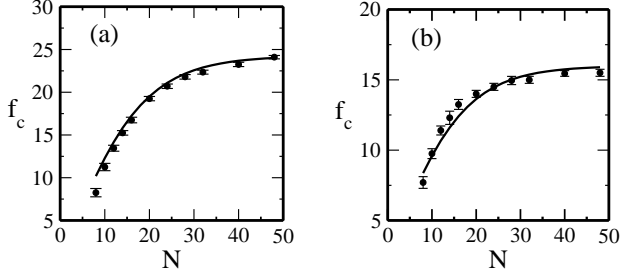


FIG. 2: Variation of rupture force with the length of dsDNA. The shearing force is applied at (a) 3'–3' ends and (b) 5'–5' ends. Solid circles (with error bars) are the data points obtained from the coarse grained simulations, whereas the solid line is obtained from the analytical expressions for the rupture force (Eqs. (24) and (25)).

of two strands. Here, we set $C = 1$ and $A = 1$. The second term of LJ potential corresponds to the base-pairing interaction between two strands. The base-pairing interaction is restricted to the native contacts ($\delta_{ij} = 1$) only, i.e., the i^{th} base of 1st strand forms pair with the i^{th} base of 2nd strand only, which is similar to the Go model [26]. The parameter $d_0 (= 1.12)$ corresponds to the equilibrium distance in harmonic potential. This is close to the equilibrium position of the LJ potential. The equation of motion is obtained from the following Langevin equation [27–30]:

$$m \frac{d^2 \mathbf{r}}{dt^2} = -\zeta \frac{d\mathbf{r}}{dt} + \mathbf{F}_c(t) + \mathbf{\Gamma}(t), \quad (4)$$

where $m (= 1)$ is the mass of a bead and $\zeta (= 0.4)$ is the friction coefficient. The parameters used in Eqs. (3) and (4) are dimensionless. Here, $\mathbf{F}_c(t)$ is given by $-\frac{dE}{d\mathbf{r}}$. The random force $\mathbf{\Gamma}(t)$ is a white noise [29], i.e., $\langle \mathbf{\Gamma}(t)\mathbf{\Gamma}(t') \rangle = 2d\zeta T\delta(t-t')$, where, d is the dimension of the space. The choice of this dynamics keeps the temperature of the system constant throughout the simulation. The equation of motion is solved by using the 6th order predictor-corrector algorithm with a time step of $\delta t = 0.025$ [29]. In averaging, different trajectories have been used and equilibrium is assured by monitoring the stability of data with a longer run.

III. DNA RUPTURE ANALYSIS

We study rupture events in the constant force ensemble [3]. We apply a constant force at the complementary

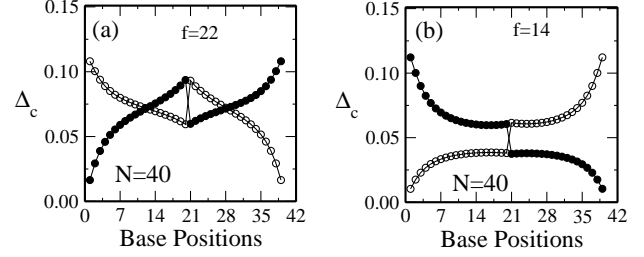


FIG. 3: Variation in the extension in covalent bonds along the chain. A shearing force is applied (a) at the 3'–3'–ends and (b) at the 5'–5'–ends. Solid and open circles correspond to the distribution of one (upper) strand and complementary (lower) strand, respectively (Fig.1). The jump occurs at the interface of the segments of different elastic constants.

ends (3'–3' and 5'–5' ends) as shown in Fig. 1. and add an energy $-\mathbf{f} \cdot \mathbf{x}$ to the total energy of the system given by Eq. (3). Here, \mathbf{x} is the elongation in DNA along the applied force direction. The rupture force is defined as a maximum force, when all the intact base-pairs break simultaneously. The most probable rupture force, obtained over many realizations, is referred as f_c [31]. Fig. 2 (a) shows the variation of rupture force with chain lengths, when the force is applied at the 3'–3'–ends, whereas Fig. 2 (b) depicts the case when the force is applied at 5'–5'–ends. It is evident from the plots that the magnitude of the force required to rupture dsDNA is higher for the ends having higher spring constant ($Q > U$). This is consistent with the hypothesis that higher force is required to stretch the stiffer bonds. It is also clear that the qualitative nature of the variation of rupture force with chain length is similar to the one seen in experiments, i.e., for small N , the rupture force increases linearly, and then saturates at higher values of N [10].

We now analyse the extension in covalent bond (Δ_c) and stretching in hydrogen bond (Δ_h) along the chain just below the rupture force. Fig. 3 shows the variation of Δ_c with base positions. There is a striking difference between the distributions when the force is applied at 3'–3'–ends (Fig.3 (a)) and 5'–5'–ends (Fig. 3(b)). It is clear that the distribution is symmetric like in previous study of homosequence of dsDNA [18], with a major change, i.e., occurrence of discontinuity at the interface of segments of diblock model of dsDNA. When the force is applied at the 3'–3'–ends, which has the larger elastic constant (Q), then the bonds near the pulling ends get stretched more, and decreases gradually. At the interface, because the net effect of force is transferring from higher elastic constant (Q) to the lower elastic constant

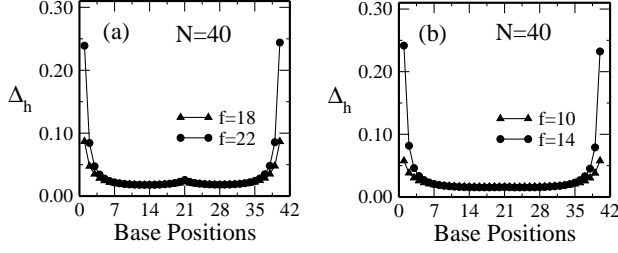


FIG. 4: Variation in extension of the hydrogen bonds Δ_h along the chain. The shearing force is applied (a) at the 3' – 3' – ends and (b) at the 5' – 5' – ends

(U) side, the extension in the bond increases at the interface ($f = -Ux$), and there is a further decrease in the extension of bond towards the other end, i.e., 5' – 5' – ends. Here, the extension is quite less compare to the extension at the middle of the strand, because no force is applied at this end. However, 5' – end has a base-pairing with 3' – end, where a similar force is applied, but in the opposite direction. As a result, we see relatively less increase in the extension. Similar nature of the curve is obtained when the force is applied at the 5' – 5' – ends (Fig. 3(b)). The only apparent change is the decrease in the extension at the interface of the segment of the diblock dsDNA. In this case the applied force is transferred from the lower elastic constant side (U) to the higher elastic constant side (Q). Fig. 4 shows the distribution of stretching in hydrogen bonds Δ_h with the base positions. The characteristic de Gennes length for the present heterogeneous system is about 10. It is clear that above this length, the differential force approaches to zero. The discontinuity at the middle is attributed to the interface effect.

IV. LADDER MODEL OF DNA

We revisit the ladder model of DNA and include the heterogeneity in the description to validate results obtained in Sec. III. Following the de Gennes formulation, we substitute the covalent bonds of adjacent nucleotides of each segment with the harmonic springs. However, instead of taking uniform value of spring constant of each strand (Fig. 1), here, we choose spring constant U for covalent bonds of the first segment of the single strand, and the spring constant Q for covalent bonds of other segment of the same strand. For the complementary strand, Q is the spring constant for covalent bonds of the first segment, while U is the spring constant for covalent bonds

of the other segment. The base-pairing interaction is also modelled by harmonic oscillator with the uniform spring constant R assuming that interactions involved in pairing are the same for the A-T and T-A base-pairs. Let the displacements of the upper and lower strands be u_n and v_n , respectively. The Hamiltonian of the composite diblock system can be written as

$$\begin{aligned}
 H = & \sum_{n=0}^{\frac{N}{2}} \frac{1}{2} Q (u_n - u_{n+1})^2 + \sum_{n=-\frac{N}{2}}^0 \frac{1}{2} U (u_n - u_{n+1})^2 \\
 & + \sum_{n=0}^{\frac{N}{2}} \frac{1}{2} U (v_n - v_{n+1})^2 + \sum_{n=-\frac{N}{2}}^0 \frac{1}{2} Q (v_n - v_{n+1})^2 \\
 & + \sum_{n=-\frac{N}{2}}^{\frac{N}{2}} \frac{1}{2} R (v_n - u_n)^2
 \end{aligned} \quad (5)$$

A shearing force may be applied either at 5' – 5' or 3' – 3' – ends (Fig. 1). The first two terms of Eq. (5) correspond to the energy contribution due to the stretching of covalent bonds of the upper strand. The next two terms are for the lower strand. The last term gives the energy contribution arising due to the stretching of the hydrogen bonds.

For $n > 0$, the equilibrium condition under the shear force for the upper strand can be written as

$$\frac{\partial H}{\partial u_n} \equiv Q(u_{n+1} - 2u_n + u_{n-1}) - R(v_n - u_n) = 0, \quad (6)$$

and similarly for the lower strand, it can be expressed as follows:

$$\frac{\partial H}{\partial v_n} \equiv U(v_{n+1} - 2v_n + v_{n-1}) + R(v_n - u_n) = 0. \quad (7)$$

If the total number of base-pairs is very large, we can consider n to be continuous, and thus, Eq. (6) and Eq. (7) can be written as

$$Q \frac{\partial^2 u_n}{\partial n^2} - R(v_n - u_n) = 0 \quad (8)$$

and

$$U \frac{\partial^2 v_n}{\partial n^2} + R(v_n - u_n) = 0. \quad (9)$$

From Eqs. (8) and (9), we obtained

$$Q \frac{\partial^2 u_n}{\partial n^2} + U \frac{\partial^2 v_n}{\partial n^2} = 0. \quad (10)$$

Since u_n and v_n are independent from each other, therefore, Eq. (10) can be expressed as

$$\frac{\partial^2 (Qu_n + Uv_n)}{\partial n^2} = 0. \quad (11)$$

Integrating Eq. (11), and the fact that the total tension is conserved, we obtained

$$Qu_n + Uv_n = nf. \quad (12)$$

Dividing Eq. (8) by Q and Eq. (9) by U , and subtracting, we get

$$\frac{\partial^2 (u_n - v_n)}{\partial n^2} - \frac{R(Q+U)}{QU} (u_n - v_n) = 0, \quad (13)$$

$$\frac{\partial^2 \delta_n}{\partial n^2} - \frac{R(Q+U)}{QU} \delta_n = 0, \quad (14)$$

where

$$\delta_n = u_n - v_n. \quad (15)$$

Equation (14) is the second order differential equation whose solution is of the form

$$\delta_n = \delta_0 \cosh(\chi n) + A \sinh(\chi n), \quad (16)$$

where $\chi^2 = \frac{R(Q+U)}{QU}$. Here, δ_0 is the elongation of the hydrogen bond at $n = 0$, and A is an arbitrary constant of integration. A similar solution exists for $n < 0$. Since the system has symmetry, the solution of Eq. (16) should also be symmetric and therefore, A will be zero. Using Eqs. (12), (15), and (16), expressions for u_n and v_n can be derived as

$$u_n = \frac{nf}{Q+U} + \frac{U}{Q+U} \delta_0 \cosh(\chi n) \quad (17)$$

$$v_n = \frac{nf}{Q+U} - \frac{Q}{Q+U} \delta_0 \cosh(\chi n). \quad (18)$$

Similar expressions for the other side of the chain, i.e., $n < 0$ can be derived as

$$u_n = \frac{nf}{Q+U} + \frac{Q}{Q+U} \delta_0 \cosh(\chi n) \quad (19)$$

$$v_n = \frac{nf}{Q+U} - \frac{U}{Q+U} \delta_0 \cosh(\chi n) \quad (20)$$

Since harmonic potentials are used to simulate the interaction between base-pairs, an additional parameter is needed to provide the condition for the rupture of hydrogen bonds. Let f_1 be the maximum force, which hold a base-pair intact, and beyond that it undergoes rupture. Thus,

$$R|u_n - v_n| \geq f_1. \quad (21)$$

The forces at the end points of the system must be balanced, which gives the expression for the force as

$$f = Q(u_{\frac{N}{2}} - u_{\frac{N}{2}-1}) + R(v_{\frac{N}{2}} - u_{\frac{N}{2}}). \quad (22)$$

Substituting the values for v_n and u_n in Eq. (22), we get

$$f = \frac{R(Q+U)}{U} \cosh(\chi \frac{N}{2}) \delta_0 (1 + \chi^{-1} \tanh(\chi \frac{N}{2})). \quad (23)$$

Using Eq. (21) and (23), we get the expression for rupture force applied at $3' - 3'$ -ends

$$\frac{f_c}{f_1} = \frac{Q+U}{U} (1 + \chi^{-1} \tanh(\chi \frac{N}{2})). \quad (24)$$

When a force is applied at the end of the complementary strand ($5' - 5'$ -ends), the rupture force would be

$$\frac{f_c}{f_1} = \frac{Q+U}{Q} (1 + \chi^{-1} \tanh(\chi \frac{N}{2})). \quad (25)$$

V. CONCLUSIONS

In this paper, we have performed Langevin dynamic simulations using a coarse grained diblock model of ds-DNA to study rupture events. We showed that magnitude of the rupture force is different when the force is applied at $3' - 3'$ and $5' - 5'$ -ends. We have studied

the distributions of extension in hydrogen and covalent bonds, which show the symmetry with a jump at the interface of the two segments. This discontinuity occurs due to the change in the elastic constants at the interface. For short chains, we find that the rupture force increases linearly, and saturates for longer chains for both cases. This is consistent with the experiment and previous studies [10, 18]. The distribution of hydrogen bonds shows that the differential force penetrates up to the de Gennes length. The numerical results have been validated with the ladder model of diblock DNA. We have obtained the analytical expression for the rupture force for both cases. It is evident from Fig. 2 that simulations data represented by solid circles are in good agreement with the analytical results (Eqs. (24) and (25)) shown by the solid line. The de Gennes length in this case found to be $\chi^{-1} = \sqrt{\frac{QU}{R(Q+U)}}$, which is in good agreement with simulation results.

At this stage, we must point out that though the model

ignores the semi-microscopic detail of dsDNA, e.g., precise description of $3' - 3'$ and $5' - 5'$ -ends, orientation and inclination of base-pairs, helical structure of dsDNA, heterogeneity in the sequence, etc., even if, it captures some essential physics of the rupture mechanism of DNA. It would be interesting to perform all-atom simulations, where above shortcomings of the model can be avoided, and one can get a better description of rupture mechanism.

VI. ACKNOWLEDGMENTS

We thank Garima Mishra and B. P. Mandal for the fruitful discussions on the subject. Financial supports from the Department of Science and Technology, and Council of Scientific and Industrial Research, New Delhi are gratefully acknowledged. The generous computer support from IUAC New Delhi is also acknowledged.

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[31] We have averaged over 25 realizations. The force has been incremented at the step of 0.5 till rupture occurs. The

standard deviation found here is less than the force interval 0.5 used in the simulation.